LETTERS TO THE EDITOR

Disagreement on the Reflex Sympathetic Activity Elicited by Experimental Coronary Occlusion

The recent paper "Interaction between cardiac receptors and sinoaortic baroreceptors in the control of efferent cardiac sympathetic nerve activity during myocardial ischemia in dogs" by Felder and Thames (1979) tends to offer a potentially misleading general view of this problem. These authors claim that the sympathetic afferents from the heart can hardly mediate a sympathetic cardio-cardiac excitatory reflex as originally described by Malliani et al. (1969), whose conclusions they question for the paucity of experiments carried out on spinal animals. However, quite surprisingly they ignore the confirmatory subsequent study by Brown and Malliani (1971) performed exclusively on spinal vagotomized animals. In both of these studies, interruption of the baroreceptive reflex by vagotomy and spinal section did not cause any increase of baseline sympathetic activity over that recorded in the intact anesthetized state, and the reduction of coronary flow could still elicit a definite excitatory reflex.

In the paper by Felder and Thames (1979), the specific search for an excitatory reflex mediated by cardiac sympathetic afferents was carried out on dogs submitted to sinoaortic denervation and vagotomy; this procedure is likely to have increased sympathetic nerve activity near the maximum (heart rate was 220 beats/min (Table 1), and this is admitted by the authors in the Discussion. It isreasonable to suggest that it was this very high baseline sympathetic activity that prevented the authors from observing the excitatory reflex. Indeed, from a careful analysis of their published data it appears that they could sometimes observe an excitatory response after sinoaortic denervation and vagotomy, and it is suggestive that the animals illustrated in Figure 3 (after vagotomy) in which this excitatory response was detectable had a lower heart rate (181 beats/min, Table 1) and were therefore likely to have a less abnormally enhanced baseline sympathetic activity. This finding was not explored further by the authors and was disregarded in the general conclusions.

There is now abundant experimental evidence that myocardial ischemia can be associated with excitatory sympathetic reflexes affecting hemodynamic variables and cardiac rhythm. In this sense, Felder and Thames should have also quoted the work by Staszewska-Barczak and co-workers (1971, 1976) and the work by Weaver and Reimann (1979). In the unanesthetized primate it has been recently found by Randall et al. (1978) that anterior descending coronary artery occlusion was always accompanied by increases in heart rate and dLVP/dt and that these changes were unlikely to reflect a simple pain response as suggested by the behavior of the animals and by the fact that the occlusion of the left circumflex produced a depressor response. Excitatory reflexes from the heart can be obtained with bradykinin, also in the presence of an intact vagal innervation (Staszewska-Barczak et al., 1976; Weaver and Reimann, 1979). Finally, cardiac arrhythmias during coronary occlusion can be in part reflexly mediated by an afferent sympathetic limb (Schwartz et al., 1976).

The importance of the whole of these data is precisely that they offer a new interpretation for the pressor responses during human myocardial infarction (Webb et al., 1972). Angina or transient myocardial ischemia can be accompanied by hypertension and tachycardia also in the absence of pain (Littler et al., 1973; Guazzi et al., 1975; Maseri et al., 1978). It is surprising that Felder and Thames quote some of these findings (Webb et al., 1972; Randall et al., 1978) but, in their conclusions, express general skepticism of the existence of excitatory reflexes mediated by cardiac sympathetic afferents. This position is not adequately supported by their negative findings and by the appraisal of the literature.

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References
Felder RB, Thames MD (1979) Interaction between cardiac receptors and sinoaortic baroreceptors in the control of efferent cardiac sympathetic nerve activity during myocardial ischemia in dogs. Circ Res 45: 728–736

Reply to the Preceding Letter

We share Dr. Malliani's concern regarding the significance of a lack of reflex response to coronary occlusion in dogs with high basal cardiac sympathetic activity resulting from sinoaortic denervation and vagotomy (Felder and Thames, 1979). In order to address this issue we have subsequently examined the influences of the cardiocardiac sympathetic reflex during coronary occlusion in animals with more physiological levels of baseline cardiac sympathetic discharge. In these experiments, the vagal and aortic nerves were sectioned and the carotid sinuses were isolated so that carotid sinus pressure could be controlled. The baseline efferent cardiac sympathetic discharge was reduced to moderate or low levels by raising the pressure in the isolated sinuses. Thus, with carotid sinus pressure raised and held constant, the cardiac sympathetic afferents were the only receptors whose activity could change during coronary occlusion. With baseline efferent cardiac sympathetic activity maintained at moderate or very low levels, we were still unable to demonstrate an excitatory reflex response to coronary occlusion. In a similar preparation, activity recorded from afferent fibers in the T3 white rami increased during coronary occlusion, providing evidence for activation of cardiac sympathetic afferent endings. The data from these experiments have been presented in abstract form (Felder and Thames, 1980) and a manuscript reporting these results in detail is in preparation.

In our view, the principal issue is the physiological significance, not the existence, of a cardiocardiac sympathetic reflex. We are well aware that Dr. Malliani and others have been able to elicit a cardiocardiac sympathetic reflex response to myocardial ischemia in spinal animals (Malliani and Lombardi, 1978). Our reservations are prompted by a consideration of the particular experimental conditions required to demonstrate even a relatively small reflex response mediated by this pathway. A similar concern has been expressed by others (Linden, 1975; Coleridge et al., 1978).

The demonstration of a cardiocardiac sympathetic reflex response to ischemia in spinal vagotomized animals (Brown and Malliani, 1971) does not establish the physiological importance of that pathway in intact animals or humans. Preganglionic cardiac sympathetic neurons are subject to a complex system of controls, including descending influences from the brain. Spinal cord section interrupts both excitatory and inhibitory bulbospinal pathways which are important determinants of the firing rate of preganglionic neurons (Wurster, 1977), and which undoubtedly compete with or modulate the input from cardiac sympathetic afferents. It has been shown that somatovisceral reflexes in the thoracic area are greatly exaggerated after cold block of the spinal cord (Dembowsky et al., 1979), and one might anticipate a similar augmentation of the cardiocardiac sympathetic reflex response in cord-sectioned animals. It is difficult to understand the significance of data obtained under conditions in which normal mechanisms of neural control are so drastically altered. Our approach has been to examine the relative influences of specific cardiovascular reflexes in a preparation in which the spinal cord remains intact and in which other reflex mechanisms are functioning. When viewed in that context, the cardiac receptors with sympathetic afferents appear to exert little influence on changes in efferent cardiac sympathetic discharge which occur during myocardial ischemia in anesthetized dogs.

Dr. Malliani cites a number of studies (besides his own) which provide evidence for excitatory cardiovascular reflex responses to myocardial ischemia. However, none of these studies show that these excitatory responses are mediated by a spinal cardiocardiac sympathetic reflex. They do serve to illustrate several of the problems inherent in the existing literature in this area of research. First, the extent to which spinal reflexes contribute to the excitatory responses mediated by cardiac sympathetic afferents remains unknown. Staszewska-Barczak (1971) demonstrated that catecholamine secretion from the adrenal medulla increases during myocardial ischemia. Since baroreceptor input was not controlled (one carotid sinus was intact and the other was used to sample blood catecholamine levels), and since the central interaction of afferent input from specific receptor groups was not considered in the design of these experiments, it is not possible to attribute the observed changes in catecholamine secretion to any particular reflex mechanism. However, spinal cord interruption at Cl completely abolished the response, suggesting that supraspinal rather than spinal mechanisms mediated this excitatory reflex. Although the study of Schwartz et al. (1976) was interpreted to implicate the cardiac sympathetic afferents in the genesis of ventricular arrhythmias during myocardial ischemia, it did not establish the central projections of these afferent fibers (i.e., spinal vs. supraspinal), so that the mechanism responsible for a reduction in premature beats after dorsal root section remains uncertain. This interpretation is also difficult because of the fact that those cardiac sympathetic afferents which traverse the ventral roots were not interrupted in this study. In the study by Randall et al. (1978), all of the unanesthetized primates.
subjected to coronary occlusion exhibited yawning behavior which may be a manifestation of a pseudo-affective response. We are hesitant to dismiss the possibility that the pressor responses observed during anterior descending occlusion in these animals might have resulted from activation of supraspinal mechanisms via cardiac sympathetic afferent fibers.

Second, the techniques of epicardial bradykinin and electrical stimulation commonly used to elicit the cardiocardiac sympathetic reflex may cause more intense stimulation of cardiac sympathetic afferents than does myocardial ischemia. Like Staszewska-Barczak et al. (1976) and Weaver and Reimann (1979), we can obtain a prominent cardiovascular reflex response by applying bradykinin to the left ventricular epicardium, even in sinoaortic denervated vagotomized dogs. In the same animals, however, coronary occlusion evokes no excitatory response (unpublished observations). Although Weaver and Reimann (1979) reported occasional pressor responses to coronary occlusion in sinoaortic denervated cats, the predominant experience has been that coronary occlusion in the cat produces depressor responses mediated by vagal afferents (Thoren, 1976; Costantin, 1969). Generalizations based upon the reflex responses to chemical or electrical stimulation of cardiac sympathetic afferents may be misleading.

Third, our present knowledge is too limited to allow meaningful speculation concerning the influence of a cardiocardiac sympathetic reflex during myocardial ischemia in humans. In the studies by Littler et al. (1973), there is no consistent pattern of ST segment elevation, pain, and hemodynamic response suggestive of a spinal cardiocardiac sympathetic reflex. There is no reason to doubt that the tachycardia and hypertension sometimes preceding pain were provoked by some stressful event which ultimately initiated the anginal attack. In this study and in the study by Maseri et al. (1978), the onset of pain routinely coincided with a further increase in arterial pressure and heart rate, suggesting that higher cerebral centers were involved in these responses. One would anticipate that humans might respond to pain or even a lesser discomfort with centrally mediated increases in sympathetic discharge to the cardiovascular system. A possible explanation for the more prominent depressor response observed during inferior infarction in man (Webb et al., 1972) is that inferior ischemia may activate larger numbers of inhibitory cardiac receptors with vagal afferents (Thames et al., 1978) which limit the influence of excitatory sympathetic reflex mechanisms.

It is not our intention to suggest that cardiac sympathetic afferents have no role in the excitatory cardiovascular responses to ischemia. Indeed, we believe that these fibers transmit pain information to higher centers which modulate sympathetic discharge to the heart and vascular system. However, a careful examination of the spinal sympathetic cardiocardiac reflex in anesthetized dogs with spinal cord and baroreflex mechanisms functioning has led us to doubt that this spinal reflex pathway is a significant determinant of the circulatory responses to myocardial ischemia.

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References

Felder RB, Thames MD (1979) Interaction between cardiac receptors and sinoaortic baroreceptors in the control of efferent cardiac sympathetic nerve activity during myocardial ischemia in dogs. Circ Res 45: 728-736
Linden RJ (1975) Reflexes from the heart. Prog Cardiovasc Dis 18: 201-221
Thoren PN (1976) Activation of the left ventricular receptors with nonmedullated vagal afferents during occlusion of a coronary artery in the cat. Am J Cardiol 37: 1046-1051
Erratum

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